

10/510890

DT04 Rec'd PCT/PTO 08 OCT 2004

In re Appln. of Tse

Application No. Unassigned (National Phase of PCT/CA03/00522)

*CLAIM AMENDMENTS*

1. (Original) A process for preparing enantiomerically enriched (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol from racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol, comprising:

(a) converting said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol to a racemic monoester intermediate by reaction with a carboxylic acid or a reactive derivative thereof;

(b) reacting said racemic monoester intermediate with an optically active acid to form a salt of said racemic monoester intermediate;

(c) crystallization of said salt to recover an enantiomerically enriched, crystalline form of said salt;

(d) neutralization of said salt to give an enantiomerically enriched form of said monoester intermediate; and

(e) hydrolysis of the enantiomerically enriched form of said monoester intermediate to produce said enantiomerically enriched (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol.

2. (Original) The process of claim 1, wherein the (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol produced in step (e) is enriched in an enantiomer which can be converted to escitalopram by dehydration and by substitution of bromine by a nitrile group.

3. (Currently Amended) The process of claim 1 or 2, wherein step (a) comprises reaction of said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol with a reactive derivative of a carboxylic acid, said reactive derivative being selected from the group comprising acid chlorides and acid anhydrides.

4. (Original) The process of claim 3, wherein said step (a) comprises reaction of said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol with acetic anhydride to form the monoacetate ester of said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol.

5. (Original) The process of claim 1, wherein said optically active acid is di-p-toluoyl tartaric acid.

6. (Original) The process of claim 5, wherein said optically active acid is (+)-di-p-toluoyl tartaric acid.

7. (Original) The monoacetate ester of (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol and salts thereof.

8. (Currently Amended) The ester of claim 7, being An enantiomerically enriched ~~monoacetate ester of (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol and salts thereof.~~

9. (Original) The ester of claim 8, being enriched in an enantiomer which can be converted to escitalopram by dehydration and by substitution of bromine by a nitrile group.

10. (Original) The ester of claim 9, wherein said salt is the (+)-di-p-toluoyl tartaric acid salt of said monoacetate ester.

11. (Original) A process for preparing escitalopram, comprising:

- (a) reacting 5-bromophthalide with 4-fluoro-phenylmagnesium bromide to produce 4-bromo-2-hydroxymethyl-4'-fluorobenzophenone;
- (b) reacting said 4-bromo-2-hydroxymethyl-4'-fluorobenzophenone with 3-dimethylaminopropyl magnesium chloride to produce racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol;

- (c) converting said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol to a racemic monoester intermediate by reaction with a carboxylic acid or a reactive derivative thereof;
- (d) reacting said racemic monoester intermediate with an optically active acid to form a salt of said racemic monoester intermediate;
- (e) crystallization of said salt to recover an enantiomerically enriched, crystalline form of said salt;
- (f) neutralization of said salt to give an enantiomerically enriched form of said monoester intermediate;
- (g) hydrolysis of the enantiomerically enriched form of said monoester intermediate to produce enantiomerically enriched (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol;
- (h) dehydration of said enantiomerically enriched (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol to produce enantiomerically enriched 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane; and
- (i) replacement of bromine by a nitrile group to produce escitalopram.

12. (Original) The process of claim 11, wherein step (c) comprises reaction of said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol with a reactive derivative of a carboxylic acid, said reactive derivative being selected from the group comprising acid chlorides and acid anhydrides.

13. (Original) The process of claim 12, wherein said step (c) comprises reaction of said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol with acetic anhydride to form the monoacetate ester of said racemic (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol.

14. (Original) The process of claim 11, wherein said optically active acid is di-p-toluoyl tartaric acid.

15. (Original) The process of claim 14, wherein said optically active acid is (+)-di-p-toloyl tartaric acid.